## REMARKS/ARGUMENTS

### I. FORMAL MATTERS

Applicants' counsel thanks Examiner Chen for granting a telephone interview on March 2, 2010, during which claims 1 and 5 were discussed with regard to the Cox reference. Also discussed were potential limitations including closed transitional terms, potential limitations directed to preferred embodiments, and Applicants' co-pending U.S. Appl. No. 10/562,866. It is believed that the amendment of the claims and the following remarks address any instructions as provided by the Examiner.

An RCE, Information Disclosure Statement, and references are being submitted herewith. Claims 1, 5, 12, and 13 are currently amended and claims 2, 10, 11, and 14 have been cancelled, all without prejudice or disclaimer subject to filing of a continuation or divisional application. New claims 15-34 have been added. No new matter has been entered. Basis for the amendments can be found in the specification as filed. Regarding claim 1 in particular, support is provided in the Specification as filed, e.g. p. 2, lines 28-31, p. 3, lines 1-11, p. 16, lines 4-8, and p. 26, lines 15-18. Regarding claim 5, support is provided in the Specification, e.g. p. 10, lines 11-20, as well as by above-notes support for claim 1. Regarding claim 24, support is provided in the Specification, e.g. p. 3, 26-29, p. 6, lines 7-17, and pp. 16-18, Example 4, Table 2, as well as by the above-notes support for claim 1. Support for claims 12 and 25 is provided in the Claims as filed, e.g. p. 27, lines 22-26. Support for claims 13 and 26 is provided in the Claims as filed, e.g. p. 27, lines 28-30, and p. 28, lines 1-2. Support for claims 15-18 and 27-30 is provided in the Specification, e.g. p. 8, lines 23-30. Support for claims 19, 20, 31, and 32 is provided in the Specification, e.g. p. 8, lines 11-21. Support for claims 21, 22, 33, and 34 is provided in the

Specification, e.g. p. 4, lines 13-16. Support for claim 23 is provided in the Specification, e.g. p. 3, lines 1-11, and pp. 16-18, Example 4, Table 2.

All pending claims encompass the elected claim group I, a composition of iscom complexes. With regard to the claims that read upon the elected species, it is to be appreciated that all pending claims also read upon elected species saponin fractions A and C.

II. REJECTION OF CLAIMS 1, 5, 12, and 13 UNDER 35 U.S.C. § 102(b)

The Examiner has maintained the rejection of claims 1, 5, 12, and 13 under 35 U.S.C. § 102(b) as being anticipated by Cox et al., WO 96/11711 (the PCT application on which Cox U.S. Pat. No. 6,352,697, also cited in this case, is based). Respectfully, as explained below, Cox does not disclose all of the limitations arranged or combined in the same way as recited in the claims as amended, i.e. a composition comprising at least two types of iscom particles, as recited in amended claim 1, new claim 24, and claims 12, 13, 15-23, and 25-34, which depend therefrom, or a kit comprising at least two parts, as recited in remaining amended claim 5, and thus Cox fails to anticipate the claims.

"[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." Net Moneyin, Inc. v. Verisign, Inc., 545 F.3d 1359, 1371 (Fed. Cir. 2008) (emphasis added); see also Ex parte Frye, Appeal 2009-006013 (B.P.A.I. 2010), at 11) ("To establish anticipation, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim." (emphasis added)).

The passages of Cox cited by the Examiner fail to disclose all of the limitations arranged or combined in the same way as recited in the claims. Specifically, the Examiner has cited Cox, WO 96/11711, page 1, lines 4-6, page 3, lines 23-25, page 10, line 19, page 15, lines 5 and 7, page 16, lines 1-3 and 11-13, Example 6, page 4, lines 1-2, page 26, claim 1, page 8, Table 1, and Example 2. As can be seen, neither these cited passages, nor any other passages of Cox, disclose the compositions of amended claim 1 or new claim 24, because the passages do not disclose any composition comprising at least two types of iscom particles, as recited in both claim 1 and claim 24, let alone such a composition wherein the first type of iscom particle comprises fraction A of *Quillaja Saponaria* Molina (hereinafter "fraction A") and not fraction C of *Quillaja Saponaria* Molina (hereinafter "fraction C"), and the second type of iscom particle comprises fraction C and not fraction A, as also recited in claim 1, nor such a composition wherein the first type of iscom particle consists essentially of fraction A and the second type of iscom particle consists essentially of fraction C, as also recited in claim 24. The passages also do not disclose the kit of amended claim 5 because, for example, the passages do not disclose any kit comprising at least two parts, as recited in claim 5, let alone such a kit wherein the first part comprises at least a first type of iscom particle that comprises fraction A and not fraction C and the second part comprises at least a second type of iscom particle that comprises fraction C and not fraction A, as also recited in claim 5.

Although the Examiner has asserted that the cited passages of Cox teach various saponin preparations and various iscom preparations, that the amounts of QH703 and Quil A confer different immunogenicity, and that preparations of Quil A, QH-C, and mixtures of QH-A and QH-C were used to make iscom matrices for dosing mice, Office action dated December 8, 2010, p. 3, and although Cox discloses various compositions, each including only a single type of

iscom particle, e.g., Cox, WO 96/11711, pp. 17-18, Table 4, for reasons already of record, e.g., Declaration of Lövgren Bengtsson, dated June 6, 2008, paras. 8-13 (discussing U.S. Pat. No. 6,352,697, the U.S. equivalent of Cox, WO 96/11711), it does not follow that Cox discloses a composition comprising at least two types of iscom particles, as recited in claims 1 and 24, or a kit comprising at least two parts, as recited in claim 5. Of note, the failure of cited Cox, WO 96/11711, Example 6 in particular to disclose a composition comprising at least two types of iscom particles is apparent from the reference in Cox Example 6 to results shown in Cox Fig. 5. As can be seen from Cox Fig. 5, the results disclose five compositions, each comprising only a single type of iscom particle, i.e. iscoms made from QH703, Quil A, QH-C, QH307, or QH 505, not any composition comprising at least two types of iscom particles, e.g. not any composition comprising both iscoms made from QH703 and iscoms made from Quil A, or any other such pair of at least two types of iscom particles. Also of note, the failure of cited Cox, WO 96/11711, page 26, claim 1 and the rest of the claims of Cox in particular to disclose any composition comprising at least two types of iscom particles is apparent from Cox claims 1-3 being directed to a saponin preparation, not a composition comprising iscom particles, Cox claims 4-7 being directed to an iscom matrix or an immunogenic iscom, not a composition comprising at least two types of iscom particles, Cox claim 8 being directed to a vaccine composition that comprises either an iscom matrix or an immunogenic iscom, not a composition comprising at least two types of iscom particles, and Cox claim 9 being directed to a method of use of the composition of Cox claim 8, not of a composition comprising at least two types of iscom particles.

Thus, for at least the reasons above, Cox fails to disclose all of the limitations arranged or combined in the same way as recited in the claims. Accordingly, the rejection of claims 1 and 5 for anticipation over Cox is respectfully submitted to be overcome. Moreover, because claims

12 and 13 depend from claim 1, Cox also fails to anticipate these claims, and accordingly the rejection of claims 12 and 13 is also respectfully submitted to be overcome. Furthermore, because new claims 15-23 also depend from claim 1, it is respectfully submitted that Cox also does not anticipate these claims. Further still, for at least the reasons above, it is respectfully submitted that Cox also does not anticipate new claim 24, nor new claims 25-34, which depend therefrom.

III. REJECTION OF CLAIMS 1, 5, 12, and 13 UNDER 35 U.S.C. § 103(a)

The Examiner has not expressly withdrawn the rejection of claims 1, 5, 12, and 13 under 35 U.S.C. § 103 as obvious over Cox et al., WO 96/11711, as stated in the Office action dated Nov. 27, 2007, pages 4-5. Respectfully, as explained below, even assuming for purposes of argument that a prima facie case of obviousness of the claims were established, the compositions of amended claim 1, new claim 24, and claims 12, 13, 15-23, and 25-34, which depend therefrom, and the kit of remaining amended claim 5 exhibit greater than expected results in terms of lower toxicity, and thus Cox fails to render obvious the claims.

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness . . . of the claims at issue." MPEP § 716.02(a)(I).

The compositions of amended claim 1 and new claim 24 and the kit of amended claim 5 exhibit greater than expected results in terms of lower toxicity. Specifically, the compositions of claims 1 and 24, which again comprise at least two types of iscom particles, the first type of iscom particle comprising fraction A and not fraction C and the second type of iscom particle comprising fraction C and not fraction A, or the first type of iscom particle consisting essentially of fraction A and the second type of iscom particle consisting essentially of fraction C,

respectively, yield greater than expected results in terms of lower toxicity in comparison to the compositions of Cox that comprise a single type of iscom particle comprising both fraction A and fraction C. As explained in more detail below, the results for the claimed compositions are greater than for the Cox compositions in terms of lower toxicity because the claimed compositions result in lower lethargy scores, lower % loss body weight, higher cytotoxic doses, lower acute toxicity, and/or higher lethal doses, in mice and/or a human macrophage cell line, across a range of doses and ratios of fractions A:C, in comparison to corresponding Cox compositions. As also explained in more detail below, the results were unexpected because Cox does not provide any basis to expect that the claimed compositions would result in lower toxicity than the Cox compositions where both compositions include fractions A and C in the same ratios and because the results are disproportional to results expected for compositions including iscom particles made from fraction A ("fraction-A iscom particles") only and observed for compositions including iscom particles made from fraction C ("fraction-C iscom particles") only.

The fact that the results were greater than expected is shown, for example, based on the following evidence, which is already of record:

- Lower lethargy score for the claimed composition versus the Cox composition (lethargy score of 2.5 versus 6), indicating better comfort, upon administration to mice of doses of 100 μg of the compositions, wherein the ratio of fractions A:C was 83:17 (i.e. claimed composition comprising two types of iscom particles, fraction-A iscom particles and fraction-C iscom particles, at a ratio of 83:17, versus Cox composition comprising iscom particles comprising a single type of iscom particle comprising both fractions A and C at a ratio of 83:17) and wherein

all iscom particles included palmitified ovalbumin antigen. Amendment dated August 24, 2009, Enclosure 2, Table 2.

- Lower % loss of body weight for the claimed composition versus the Cox composition (% loss body weight of 10.4% versus 15.7%), also upon administration to mice of doses of 100 μg, wherein the ratio of fractions A:C was 83:17 and wherein all iscom particles included palmitified ovalbumin antigen. Amendment dated August 24, 2009, Enclosure 2, Table 2.
- Higher cytotoxic dose for the claimed composition versus the Cox composition (LC50 μg/ml of >240 versus 18.711), upon administration to human macrophage cell line U937, wherein the ratio of fractions A:C was 10:1 for the claimed composition (i.e. including fraction-A iscom particles and fraction-C iscom particles at a ratio of 10:1) versus 7:3 for the Cox composition (i.e. including iscom particles comprising both fractions A and C at a ratio of 7:3) and wherein the iscom particles corresponded to iscom matrix particles. Amendment dated August 24, 2009, Enclosure 3, Table 1.
- Lower acute toxicity for the claimed compositions at various ratios of fractions A and C versus the Cox compositions at corresponding ratios (lethality # of 2/8, 0/8, and 0/8 versus 8/8, 6/8, and 5/8), upon administration to BALB/c mice of doses of 50 μg, wherein the ratios of fractions A:C were 8/2, 9/1, and 9.5/0.5 and wherein the iscom particles corresponded to iscom matrix particles. Amendment dated August 24, 2009, Enclosure 4, Table titled "Acute toxicity in BALB/c mice;" see also Specification as filed, p. 17, Table 2, group nos. 1-3 versus 8-10 (presenting

same results); Declaration of Lövgren Bengtsson dated June 6, 2008, paras. 16-18 (discussing the results).

- "The lethal dose[s] for BALB/c mice were substantially (five-fold or more) reduced when comparing administration of conventional mixtures of Fraction A and Fraction C together in matrix according to the Cox patent," i.e. in a single type of iscom particle, "compared with comparable amounts of mixtures of Fraction-A matrix and Fraction C matrix according to the present invention," i.e. mixtures of two types of iscom particles. Declaration of Lövgren Bengtsson, para. 24.

The fact that the results were greater than expected is based, for example, on a lack of any teaching or suggestion in Cox that the claimed compositions would result in lower toxicity than the Cox compositions. As discussed above, Cox does not disclose any composition comprising at least two types of iscom particles, let alone any composition comprising fraction-A iscoms and fraction-C iscoms, and thus does not provide any direct teaching regarding toxicity thereof. Cox also does not present any data directly addressing toxicity of the Cox compositions in comparison to other compositions. Of note, in contrast to data presented above regarding weight loss and acute toxicity, the weight loss and % survivors data as presented in Cox Table 4 relate to efficacy in the context of aerosol challenge, not toxicity. See Cox, WO 96/11711, p. 16 ("These iscom preparations were also less protective as shown by less than 100% protection on subsequent challenge. Significant weight loss was also shown by survivors in group 1; the extent of weight loss being a further indicator of the level of protection afforded by vaccination."). Also of note, in contrast to the data presented above regarding lethargy scores, % loss body weight, cytotoxic doses, acute toxicities, and lethal doses, the data regarding haemolytic activity

as presented in Cox Example 7 does not correlate well with toxicity, at least with regard to fraction C. See Amendment dated August 24, 2009, pp. 6-7 (discussing actions taken by CSL and the Drane reference). To the extent that Cox discusses conclusions from toxicity analyses of the preferred Cox composition, the conclusions are ambiguous. See Declaration of Lövgren Bengtsson, para. 14 (explaining that dose levels thereof used with mice in Cox were only 2-5 fold lower than the lethal dose of 1.4 mg/kg reported in Cox and that the comparatively high IL-1 production associated therewith can be compatible with the surprisingly high toxicity that has been observed). Although Cox teaches an advantage associated with compositions comprising both fractions A and C, the advantage is based on making a single type of iscom particle from fractions A and C, and thus would not be expected for compositions, as claimed in claims 1 and 24, or a kit as claimed in claim 5, that instead comprise distinct fraction-A iscoms and fraction-C iscoms. More specifically, Cox teaches that making a single type of iscom particle from fractions A and C is advantageous relative to making iscom particles from either fraction A alone or fraction C alone, the advantage being based on balancing the very high iscom-forming ability of fraction A with the high adjuvant activity of fraction C and on controlling the ratio of antigen:adjuvant in the resulting iscom particles. See Cox, WO 96/11711, p. 8, lines 1-9 (the lines below Table 1), Table 1, p. 21, lines 31-32; see also, Declaration of Lövgren Bengtsson, paras. 5-6 (discussing the Cox patent). This advantage would not be expected for the compositions of claims 1 and 24 or the kit of claim 5, since the claimed compositions and kit are based on making distinct fraction-A iscoms and fraction-C iscoms, an approach that would exclude using the very high iscom-forming ability of fraction A to promote formation of iscoms comprising both fractions A and C and that would exclude using a mixture of fractions A and C to control the ratio of antigen:adjuvant in the resulting types of iscom particles. Accordingly, the

greater results for the claimed compositions relative to the Cox compositions were unexpected in view of Cox.

The fact that the results were greater than expected is also based, for example, on the disproportionality of the lower toxicity exhibited by the claimed compositions in comparison to compositions including fraction-A iscom particles only and compositions including fraction-C iscom particles only. As a preliminary matter, fraction-C iscom particles would have been expected to exhibit higher toxicity than fraction-A iscom particles, because for example fraction-C saponin toxicity was known to be an issue, particularly with sensitive animals such as mice, and because fraction-A saponins were known to be virtually non-toxic. See Declaration of Lövgren Bengtsson, para. 5. Accordingly, to the extent that the claimed compositions might conceivably have been expected to exhibit a level of toxicity different than those of the corresponding Cox compositions, the claimed compositions would have been expected to yield toxicity results proportional to the additive effects of the toxicities of the fraction-A iscom particles and the fraction-C iscom particles in the compositions. Instead, the toxicity exhibited by the claimed compositions was disproportionately lower than expected, as shown for example by the following evidence:

- "It should be noted that fraction-C in a MATRIX-MIX formulation," i.e. the claimed composition wherein the iscom particles are iscom matrix particles, "can be given in 13 fold higher doses than given in a solitary MATRIX-C formulation," i.e. a composition including only fraction-C iscom matrix particles. Amendment dated August 24, 2009, Enclosure 3, p. 1 and Table 1.
- Fraction C could be administered in 2 to 4-fold higher concentrations to the human macrophage cell line U937 in the claimed composition (i.e. as fraction-C

> iscom matrix particles in a composition also including fraction-A iscom matrix particles) than in a composition including only fraction-C iscom matrix particles, without reaching the LC50 cytotoxic concentration for the claimed composition. Amendment dated August 24, 2009, Enclosure 3, p. 1 and Fig. 3.

Accordingly, the greater results for the claimed compositions relative to the Cox compositions were also unexpected in view of the disproportionality of the lower toxicity of the claimed composition in comparison to toxicities expected for compositions including fraction-A iscom particles only and observed for compositions including fraction-C iscom particles only.

Although the Examiner has argued that "the result in the response shows fatality only with ISCOM-C (Enclosure 2)," and thus does not show a result sufficiently surprising to render the claimed composition non-obvious over Cox, Office Action dated December 8, 2009, p. 4, as discussed above the lower toxicity of the claimed compositions relative to the Cox compositions is apparent based on factors in addition to lethality, e.g. lower lethargy scores, lower % loss of body weight, higher cytotoxic doses, and higher lethal doses.

Also, although the Examiner has argued that "the result in the Enclosure 2, page 2, shows ISCOM A + ISCOM C at 83:17 ratio, which is not commensurate in scope with the claimed concentration of 50%-90% by weight of fraction A of Quil A and from 50%-10% by weight of Fraction C of Quil A," Office action dated December 8, 2009, p. 4, a skilled artisan would be able to ascertain a trend in the results that the claimed compositions would exhibit unexpectedly lower toxicity across a broad range of ratios of fractions A:C that would allow the skilled artisan to extend the probative value of the results, and thus, even assuming a prima facie case for obviousness of the compositions of claims 1 and 24 and the kit of claim 5, the results are sufficient to rebut a prima facie case. "When considering whether proffered evidence is

commensurate in scope with the claimed invention, Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition." MPEP § 2145 (citing In re Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987)). "For example, a showing of unexpected results for . . . a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan 'could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof.'" MPEP § 2145 (citing In re Clemens, 622 F.2d 1029, 1036 (C.C.P.A. 1980).

A skilled artisan would be able to ascertain a trend in the results that the claimed compositions would exhibit unexpectedly lower toxicity relative to the Cox compositions across a broad range of ratios of fractions A:C because, as indicated above, the results demonstrate unexpectedly lower toxicity across a specified range of ratios of fractions A:C, i.e. 8/2 to 9.5/0.5, as well as at specific ratios of fractions A:C, e.g. 83:17 and 10:1, and because the difference in toxicity between the claimed compositions and the Cox compositions remains substantial even near the endpoints of the specified range (e.g. lethargy score of 2.5 for the claimed composition versus 6 for the Cox composition, upon administration to mice of doses of 100 μg of the compositions, wherein the ratio of fractions A:C was 83:17, as indicated above). This trend would allow the skilled artisan to extend the probative value of the results because, having learned from the present application that the claimed compositions exhibit a desirable lower toxicity relative to the Cox compositions, the skilled artisan could readily design compositions having ratios of fractions A:C outside the specified range that would still exhibit the desirable lower toxicity. This is particularly so regarding new dependent claims 15-18 and 27-30, which include limitations that fraction A and fraction C account for 75% to 99.5% by weight and 25% to 0.5% by weight, respectively (claims 15 and 27), 90% to 99% by weight and 10% to 1% by

weight, respectively (claims 16 and 28), 91% to 98% by weight and 9% to 2% by weight, respectively (claims 17 and 29), and 92% to 96% by weight and 4% to 8% by weight, respectively (claims 18 and 30), of the sum of weights of fraction A and fraction C in the compositions. Thus, even assuming a prima facie case for obviousness, the results are sufficient to rebut a prima facie case with regard to claims 15-18, 27-30, and indeed for claims 1 and 24 as well as claim 5 and thus for the remaining claims too.

In addition, independent of the arguments above regarding lower toxicity, the claimed compositions also result in a synergistic effect in the adjuvanted antibody response that also would not have been expected based on Cox. Amendment dated May 27, 2008, p. 9; Declaration of Lövgren Bengtsson, para. 29-32. Specifically, the magnitude of the IgG1 response is increased, and pronounced features of both TH1 (IFN gamma and IgG2a antibody subclass) and TH2 (IL-5 and IgG1 antibody subclass) type of immune responses result. Amendment dated May 27, 2008, p. 9; Declaration of Lövgren Bengtsson, para. 29-32. For these additional reasons too, even assuming a prima facie case for obviousness of the compositions of claims 1 and 24 and the kit of claim 5, the results are sufficient to rebut a prima facie case.

In view of the Applicants showing of greater than expected results in terms of lower toxicity, it is respectfully submitted that Cox fails to render obvious the claims. Accordingly, the rejection of claims 1 and 5 for obviousness over Cox is respectfully submitted to be overcome. Moreover, because claims 12 and 13 depend from claim 1, Cox also fails to render obvious these claims, and accordingly the rejection of claims 12 and 13 is also respectfully submitted to be overcome. Furthermore, because new claims 15-23 also depend from claim 1, it is respectfully submitted that Cox also does not render obvious these claims. Further still, for at least the

reasons above, it is respectfully submitted that Cox also does not render obvious new claim 24, nor new claims 25-34, which depend therefrom.

## IV. REQUEST FOR RECONSIDERATION AND THAT APPLICATION BE ALLOWED

In view of the foregoing, Applicants respectfully request reconsideration, submit that the present application is in a condition for allowance, and request notice to that effect. If it is determined that the application is not in a condition for allowance, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge the same to our Deposit Account No. 16-0820, our Order No. ALBI-46418.

Respectfully submitted,
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